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BARBITURIC ACID AND ITS DERIVATIVES

BY

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

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BARBITURIC ACID AND ITS DERIVATIVES.

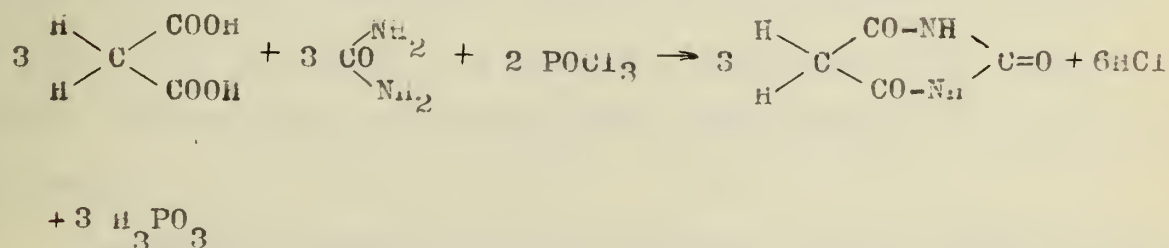
Introduction,

One of the unfortunate phases of the world war has been the withdrawal from the market of all German-made drugs and chemicals. Important among these is Veronal, one of a group of essential synthetic remedies whose manufacture in the country has become a matter of vital importance.

The primary object of the present work has been to investigate the method of manufacture of Veronal devised by Fischer and Dilthey, namely the condensation of diethyl malonic ester with urea in the presence of sodium ethylate, with a view toward increasing the yield.

Historical and Theoretical Part.

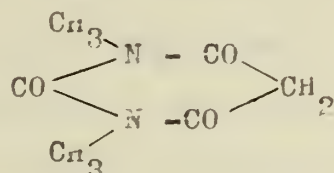
Barbituric acid was first synthesized by Grimaux¹ in 1879 by treating a mixture of equal parts of malonic acid and urea with phosphorus oxychloride.



Arthur Michael², while investigating the uses of sodium malonic ester in organic syntheses, prepared barbituric acid as one of his derivatives. He treated finely divided urea with an alcoholic solution of sodium malonic ester. A finely divided

crystalline precipitate separated which upon analysis proved to be the same as the barbituric acid made by Grimaux.

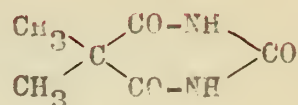
E. Muider³ prepared dimethyl barbituric acid from dimethyl urea, phosphorus oxychloride and malonic acid. To this compound he assigned the formula



Conrad and Guthzeit⁴ prepared ethyl barbituric acid from ethyl malonic acid, carbamide and phosphorus oxychloride. Furthermore they prepared the dimethyl barbituric acid by means of the diargentic derivative of barbituric acid. The latter was obtained as a red flocculent precipitate by the addition of silver nitrate to the acid ammonium barbiturate. The dimethyl and diethyl barbituric acids were made by heating the diargentic barbiturate with methyl or ethyl iodide and methyl alcohol. To determine the constitution of their substance Conrad and Guthzeit saponified it with strong potassium hydroxide. Ammonia was evolved, and on acidifying the alkaline residue and extracting with ether, an acid was found which gave analytical results corresponding to dimethyl malonic acid. Evidently the dimethyl barbituric acid made by Mulder was not the same as the derivative obtained by Conrad and Guthzeit.

In order to explain this discrepancy, Thorne⁵ prepared dimethyl malonic acid by the method described by Conrad⁶ for preparing substituted malonic esters. Furthermore he prepared dimethyl barbituric acid from dimethyl malonic acid and urea after the method originally used by Grimaux for barbituric acid. He

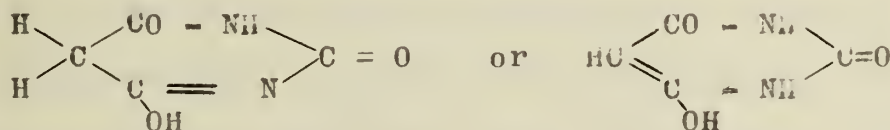
proved by the above experiments that the formula



assigned by Conrad for dimethyl barbituric acid was correct, that the first two hydrogen atoms replaced in barbituric acid in the formation of its salts are those contained in the CH_2 group of the malonyl radical and not as was formerly believed those attached to the two nitrogen atoms. It is only after the replacement of the former that the latter become capable of replacement.

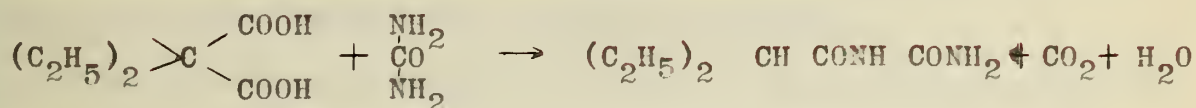
Wood and Anderson⁷ in working on the constitution of the salts of barbituric acid found that barbituric acid was considerably stronger than acetic acid. Such a value for the dissociation constant would be quite high were the acidity due simply to the hydrogen of one of the imino groups. It was shown by Wood, however, that most of the acidity was to be traced to the methylene group, the C-dialkyl barbituric acids having dissociation constants less than one thousandth of that of the parent substance.

Hantzsch and Voegelen⁸ from determinations of the electrical conductivity of solutions of barbituric acid had come to the conclusion that barbituric acid was a pseudo acid, but were unable to decide whether the acid when in solution had the formula



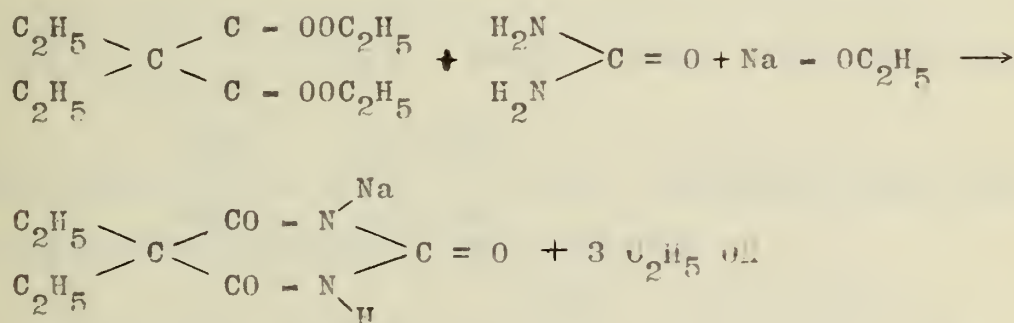
Von Mering attempted to make diethyl barbituric acid by a method similar to the one used by Grimaux i.e. urea, malonic acid and phosphorus oxychloride. Upon analysis, however, he found that his compound was not a derivative of barbituric acid but rather

ureid of diethyl acetic acid.



Phosphoruspentachloride, thionyl chloride, sulfuryl chloride, sulfonyl chlorides, and finally organic acid chlorides such as acetyl chloride, act similarly to phosphorus oxychloride.

Instigated by these facts, Fischer and Diltthey⁹ set out to find a more convenient method of making diethyl barbituric acid than that of Conrad and Guthzeit who used silver barbiturate and methyl iodide. They followed the procedure of Michael using diethyl malonic ester and urea with sodium ethylate as a condensing agent.



The role of the sodium ethylate is here simply a condensing agent as it is in many other condensations of neutral acid esters.

They prepared a long list of derivatives by this method substituting sulfurea, monoalkyl urea, and guanidin. The members of this class showed strong hypnotic effects, so they were tested physiologically by Fischer and von Mering¹⁰.

The investigations were very instructive concerning the influence of an accumulation of alkyl groups and the effect of

the size of the radical and the effect of the constitution of the ring in the production of narcotic effect.

The experiments were carried out on dogs. It was observed that there was no sleep producing effect among the dialkylated acids until the urea group was introduced. Neither diethyl acetic acid $(C_2H_5)_2 = C H COOH$, diethyl malonic acid $(C_2H_5)_2 = C >(COOH)_2$ nor diethyl (oxalic) acid $(C_2H_5)_2 = C(OH) COOH$ exerted any narcotic effect whatever. Similarly, the mono-alkyl barbituric derivatives do not have any appreciable effect. Mono-ethyl malonyl

urea
$$\begin{array}{c} C_2H_5 \\ \diagup \\ C \\ \diagdown \\ H \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array} \begin{array}{c} CO-NH \\ CO-NH \end{array} > C=O$$
 has no effect. The same is

true of mono propyl malonyl urea
$$\begin{array}{c} C_3H_7 \\ \diagup \\ C \\ \diagdown \\ H \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array} \begin{array}{c} CO-NH \\ CO-NH \end{array} > C=O.$$

Of the dialkyl derivatives, dimethyl malonyl urea

$$\begin{array}{c} CH_3 \\ \diagup \\ C \\ \diagdown \\ CH_3 \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array} \begin{array}{c} CO-NH \\ CO-NH \end{array} > C=O$$
 had no action, but methyl-ethyl

malonyl urea
$$\begin{array}{c} C_2H_5 \\ \diagup \\ C \\ \diagdown \\ CH_3 \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array} \begin{array}{c} CO-NH \\ CO-NH \end{array} > CO$$
 produced sleep after one hour and lasting throughout the whole day.

Methyl propyl malonyl urea
$$\begin{array}{c} CH_3 \\ \diagup \\ C \\ \diagdown \\ C_3H_7 \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array} \begin{array}{c} CO-NH \\ CO-NH \end{array} > CO$$

produced a transient drowsiness.

Diethyl malonyl urea (veronal)
$$\begin{array}{c} C_2H_5 \\ \diagup \\ C \\ \diagdown \\ C_2H_5 \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array} \begin{array}{c} CO-NH \\ CO-NH \end{array} > CO$$

produced sleep after thirty minutes and lasting twenty-four hours,

Veronal¹¹ has attained a very great clinical importance and is now perhaps more widely used than any other hypnotic drug, It is used as a hypnotic in simple insomnia and in the sleeplessness of hysteria, neurasthenia, mental disturbances and im-

pending delirium tremens.

The margin between the ordinary therapeutic dose (.5 gm.) and the toxic dose (8-10 gm.) is quite large so that it is a very safe drug, although there have been fatal cases of veronal poisoning from comparatively small doses. The compound is excreted by the kidneys unchanged in composition.

Veronal is a white crystalline powder melting at 191° and is odorless and faintly bitter in water solution. It is soluble in 145 parts cold water and 12 parts of hot water. It is quite soluble in ether, acetone and ethyl acetate; also slightly soluble in chloroform, petroleum benzene, acetic acid and amyl alcohol. Prolonged heating with sodium carbonate liberates ammonia. It forms salts with alkalies which are soluble in water.

Sodium diethyl barbiturate, or veronal sodium $(C_2H_5)_2$

$\begin{array}{c} \text{Na} \\ \diagup \\ \text{CO-N} \\ \diagdown \\ \text{CO-NH} \end{array} > \text{C} = \text{O}$ is used quite extensively in place of veronal because of its greater solubility, a factor that favors rapid assimilation.

Ethyl-propyl malonyl urea $\begin{array}{c} C_2H_5 \\ \diagup \\ \text{C} \\ \diagdown \\ C_3H_7 \end{array} < \begin{array}{c} \text{CO - NH} \\ \diagdown \\ \text{CO - NH} \end{array} > \text{CO}$

produced a deep sleep after 1 hour and lasting 24 hours.

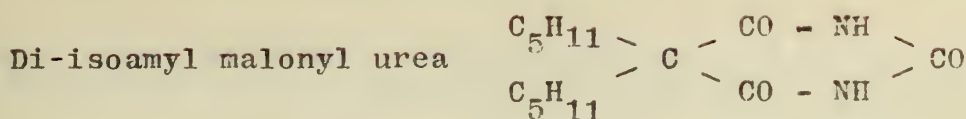
Dipropylmalonyl urea (propanol) $\begin{array}{c} C_3H_7 \\ \diagup \\ \text{C} \\ \diagdown \\ C_3H_7 \end{array} < \begin{array}{c} \text{CO - NH} \\ \diagdown \\ \text{CO - NH} \end{array} > \text{CO}$

when administered in two grain doses resulted in death; however this toxic effect was not observed after purifying the propanol,

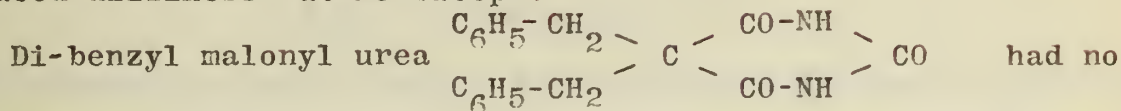
Di-isobutyl malonyl urea $\begin{array}{c} C_4H_9 \\ \diagup \\ \text{C} \\ \diagdown \\ C_4H_9 \end{array} < \begin{array}{c} \text{CO - NH} \\ \diagdown \\ \text{CO - NH} \end{array} > \text{CO}$ produced

a heavy intoxication for three minutes followed by eight hours sleep.

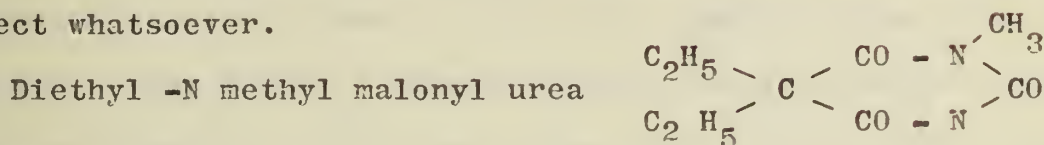
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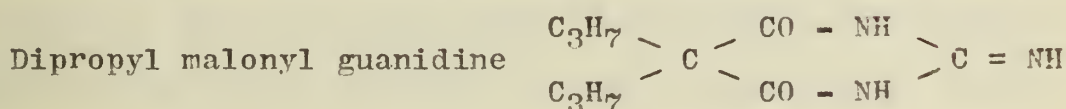
produced dizziness but no sleep .



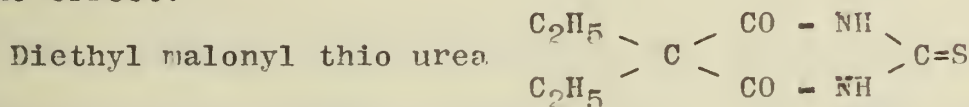
effect whatsoever.



produced a deep sleep for two days which resulted in death.



had no effect.



resulted in death after eight hours.

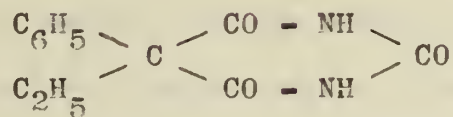
The conclusions drawn from the above experiments were, that it was essential that there be in the compound a group that contains several alkyl radicals rich in carbon.

The narcotic effect increases with the rising carbon content of the radicals up as far as propyl and after that the effect again diminishes.

A very striking phenomenon is the toxic effect produced by introducing a methyl group on one of the nitrogen atoms and likewise upon introducing sulfur in place of oxygen. On the other hand the toxic effect is not observed after introducing NH in place of oxygen.

In general the aliphatic radicals are more active sleep producers than the aromatics but this does not hold true in the case

of phenyl ethyl barbituric acid or luminal:



This compound is much stronger than veronal but must be used with care since its toxic dose is quite low. Impens claims that the hypnotic action of the aromatic radical can take effect only when there is attached to the same carbon atom with it, one or two other alkyl groups.

Perhaps the most recent work on barbituric derivatives is that of Rising and Stieglitz¹², on the preparation of phenyl-ethyl barbituric acid.

This synthesis cannot be carried out in the same way as the other derivatives because of the fact that the phenyl group cannot be introduced into the malonic ester by the customary malonic ester synthesis. The method of procedure followed was, in substance this:- Ethyl oxalate is condensed with the ethyl ester of phenyl acetic acid to form diethyl ester of oxalyl phenylacetic acid. Next the dimethyl oxalyl phenylacetic ester is converted by heat into the methyl ester of phenyl malonic acid. The ethylation of phenylmalonic methyl ester is carried out by means of ethyl iodide and sodium ethylate. The condensation of the ethyl phenyl malonic dimethyl ester with urea is carried out as in the method of Fischer and Dilthey⁹.

In view of the fact that benzyl ethyl barbituric acid could be much more conveniently synthesized than the phenyl ethyl derivative, it has been in part the object of this work to prepare the former. The testing of the physiological action must needs

be left to laboratories equipped for such investigations.

Another general method for the preparation of CC-dialkyl barbituric acids used by Fischer and Dilthey, was that in which dialkyl malonyl chloride was condensed with urea according to the equations,



The reaction was carried out at a water bath temperature and quite satisfactory yields were obtained. The dialkyl malonyl chloride was prepared from dialkyl malonic acid and phosphorus pentachloride.

Experimental Part.

Preparation of Diethyl Malonic Ester.

The method used for the preparation of diethyl malonic acid ester is essentially the same as given by Conrad¹³.

201.3 grams of sodium were dissolved in 3 liters of absolute alcohol in a five liter round bottom flask. 700 grams of malonic ester were added, and after thoroughly mixing, 1000 grams of ethyl bromide were added very slowly by means of a dropping funnel and the mixture was shaken constantly during the addition. Considerable heat was evolved so that a very efficient condenser was used to prevent the loss of alcohol and ethyl bromide. The mixture was allowed to stand over night or until the reaction was complete as was indicated by neutrality to litmus paper. Most

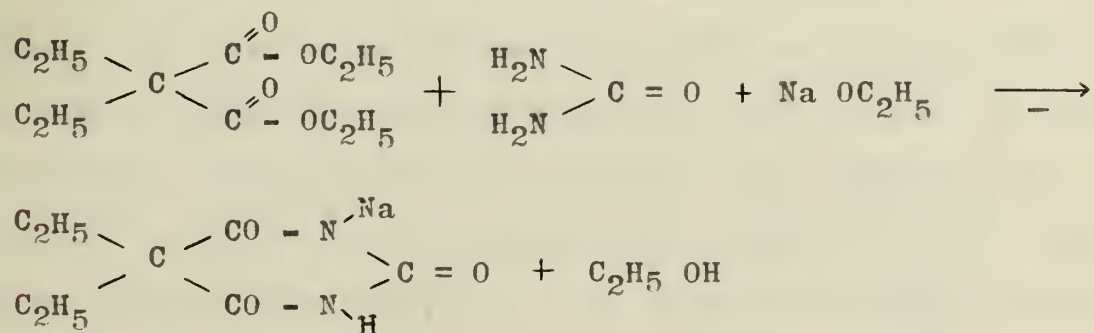
of the alcohol was distilled off on a water bath. The sodium bromide formed in the reaction formed an almost solid mass in the flask. About one liter of water was added to the contents of the flask or at least enough to dissolve the sodium bromide. The saturated sodium bromide solution salted out the diethyl malonic ester which separated as an oily layer. The latter was separated and distilled under diminished pressure.

Considerable trouble was caused by the sodium bromide which was in solution in the alcohol and which precipitated out as soon as the alcohol had distilled over. This precipitate caused very severe bumping so that it was necessary to filter it off.

About twenty millimeters of pressure were used and the product came over at 120-125°. The yield amounted to 700 grams.

Preparation of Diethyl Barbituric Acid or Veronal (2-4-6 trioxo 5,5 diethyl pyrimidine)

The procedure first used in the preparation of veronal was the one given by Fischer and Diltney⁹ and which is analogous to the method of Michael² for the preparation of barbituric acid. The reactions involved are,



Theoretically one mole of sodium would be enough for each mole of ester used but practically this amount has been found to be insufficient. In the procedure used three moles of sodium were used. Furthermore the urea as in the case of most amides, in the strong alkaline solution breaks down into NH_3 and Na_2CO_3 so that an excess over the theoretical amount must be used.

In the first run made, 16 grams of sodium were dissolved in 300 grams of absolute alcohol. After cooling, 50 grams of diethyl malonic ester were added and finally 20 grams of finely ground urea were dissolved in the mixture. The liquid became quite viscous and upon gentle warming assumed a thick milky appearance. Part of the batch was sealed in hard glass bomb tubes and the rest placed in glass pressure bottles carrying a porcelain stopper and red rubber gasket. The bombs were heated in a cotton seed oil bath for five hours at a temperature of $103-108^\circ$. Very soon after reaching the above named temperature a white crystalline precipitate of sodium carbonate separated. The bombs after cooling were allowed to stand eight hours before opening, but this practice must be avoided because on standing a very fine amorphous precipitate comes down which interferes very seriously with proper filtration. Upon opening the bombs very little pressure was noticed and apparently the pressure bottles worked as well as the bomb tubes. A red coloration of the precipitate was noticed due to the red rubber gasket, but upon precipitating the veronal the color disappeared. The precipitate was sucked dry, washed with a small amount of alcohol and then enough water added to form a thick paste. The acid was precipitated by concentrated HCl . A very violent effervescence occurred due to liberation of CO_2 from the

Na_2CO_3 . The white precipitate which separated was filtered and recrystallized from hot water but very little veronal was found after the first recrystallization. Evidently most of the precipitate which was supposedly veronal, was common salt because the mother liquors tasted very salty. The alcoholic mother liquors were evaporated almost to dryness and concentrated HCl added to them. Some veronal precipitated but was of a very dark brown color, which color could not be removed by recrystallization. The veronal upon recrystallizing three times from water came down in large pure white crystals, melting at 191° .

The melting points after the various recrystallizations were:-

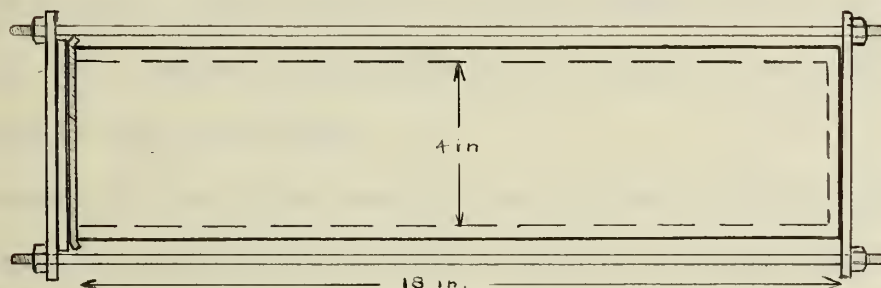
After 1st. recrystallization				M.P. 186°
"	2nd.	"	"	M.P. 188°
"	3rd.	"	"	M.P. 191°

Experiment 1.

It was surmised that perhaps the cause of the very small yield of veronal might be due to the method of precipitating the acid from the sodium salt of barbituric acid. Another run was made using the same proportions as before except that instead of filtering off the precipitate after heating, the whole content of the bombs was placed in a beaker and evaporated to a small volume on a water bath and then acidified with concentrated HCl. A considerable amount of veronal came down but was of a very dark brown color. This color was removed with very great difficulty and only after repeated boiling and recrystallizing with bone black, which process reduced the yield to a minimum.

Experiment 2.

In order to obviate the necessity of using glass bombs and to permit the use of larger amounts of substances, an autoclave was devised and constructed according to the following plan.

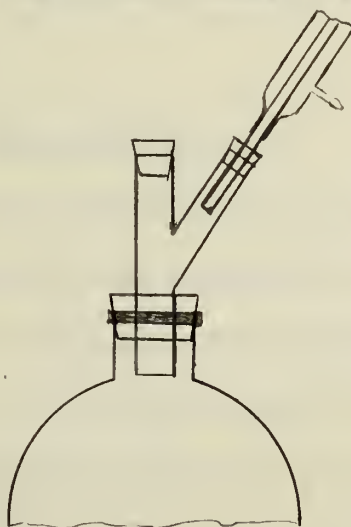


A four inch steam pipe was used for the body of the bomb and a one-half inch circular bottom was welded in with an oxy-hydrogen blow torch. The top was machined off square and a $\frac{3}{8}$ inch steel disk of a diameter somewhat larger than the pipe so that it extended over the edge $\frac{1}{4}$ inch, was used as a cap for the bomb. The cap was clamped to the bomb by means of two half inch steel rods threaded at both ends and fitted with burrs for tightening. These bolts extended through steel plates $\frac{1}{4}$ inch thick, two inches wide and fitting over the ends of the bomb. The joint was made tight with a rubber gasket of the same diameter as the cap of the bomb. As will be noted, considerable difficulty was ex-

perienced on the first trial in keeping the bomb tight, but this was due to the fact that instead of welding the bottom of the bomb, an attempt was made to merely thread it and screw on a cast iron cap.

This autoclave had a capacity of about four liters and was heated in an oil bath made from galvanized sheet iron of such dimensions that the bomb fitted in very loosely. The bath was covered on sides and bottom with sheet asbestos and supported by iron ring stands. When heated by three bunsen burners with fish tail tops, the temperature could be held quite constant by proper regulation of the gas flow.

Because of the large amounts of sodium ethylate which were used in the investigation a sodium couple was devised. A piece of glass tubing, one inch in diameter was blown out on one side and a tube of somewhat smaller diameter was welded in.



The sodium, in the form of shavings or wire was dropped in through the straight arm, thus avoiding the troublesome practice of dropping it through the condenser. Furthermore the slant given to the condenser allowed the condensed alcohol to run back

smoothly into the flask. In the case of a vertical condenser the condensed liquid, during violent refluxing, would often completely fill the condenser tube and blow out the top.

A larger run was made using 48 grams of sodium, 900 grams of absolute alcohol, 150 grams of ester, and 60 grams of urea. The mixture was placed in the steel bomb described above, but considerable difficulty was experienced in making the bomb tight so that it was not until three days after the components were mixed that they were finally heated for five hours at 125-130°. On opening the bomb the contents had formed a semisolid mass of a white solid which was filtered, taken up in enough water to make a paste and HCl added until the solution reacted acid to litmus. It was then allowed to stand over night and filtered. On acidifying the filtrate further a beautiful white precipitate of veronal came down. Forty grams of product resulted from this run, or about 31% of theory.

Experiment 3.

Following the above experiment two unsuccessful runs were made from which practically no product was isolated. The procedure was practically the same as in Experiment 1, and after heating, the contents of the bomb appeared perfectly normal, but no veronal was obtained. The cause for the failure of these runs was probably due to inferior reagents used.

Experiment 4.

An attempt was made using 2 moles of sodium instead of three and the procedure followed as in Experiment 1 except that

the mixture was allowed to stand for twelve hours before heating. It was then heated for six hours at 115° and the sodium salt decomposed with concentrated HCl. 21 grams of product were secured which corresponds to 25% of theory.

Experiment 5.

In the next run 4 moles (42.5 gms.) of sodium with 100 grams of ester were used. Only about 4 grams of veronal were isolated from this run.

Experiment 6.

A run was next made according to the original proportions ie. 32 grams Na, 100 grams ester, 40 grams urea, and 600 grams alcohol. The mixture was allowed to stand 12 hours, then heated in an autoclave for 6 hours at $115-120^{\circ}$. After opening and filtering off the white solid the latter was extracted with water for several hours and filtered. The filtrate was acidified and very little effervescence occurred indicating that very little Na_2CO_3 had gone into the solution. 15 grams of veronal resulted from this acidification. The extraction with water was repeated and a moderate evolution of CO_2 occurred upon acidifying. 7 grams of veronal resulted. The residue on acidifying proved to be almost entirely Na_2CO_3 and very little veronal was isolated from it. The total yield was 23 grams or 28% of theory.

The carbamide used in this experiment was of a technical grade manufactured by the American Cyanamid Company.

Experiment 7.

An attempt was made next, to use methyl alcoholate as a condensing agent. The components were mixed as in Experiment 1 except that equivalent amounts of methyl alcohol were used instead of ethyl alcohol. The mixture was heated for 8 hours in a boiling water bath in the steel bomb. On opening, there was very little of the white Na_2CO_3 precipitate present. The precipitate was filtered, dissolved in a small amount of water and precipitated with HCl as usual and 32 grams of product obtained. The mother liquors of methyl alcohol were allowed to stand for 6 days, then a small amount removed and the rest evaporated to dryness on a steam cone and upon acidifying 12 grams of veronal obtained, thus making a total of 44 grams. The element of time seemed quite important. The small fraction mentioned above was placed in a glass pressure bottle, wrapped in towels and heated on a steam cone. After 5 hours heating the bomb blew up with great violence, but being wrapped in towels the glass did not do any damage. The added pressure was probably due to NH_3 formed as a side product from the urea and alkali.

The use of methyl alcoholate presents some advantages over ethyl alcoholate. The smaller molecule decreases the volume of the batch and so increases the capacity of the apparatus used, and because of the lower boiling point of the methyl alcohol, a pressure sufficient to make the reaction go, can be attained by simply heating the bomb in a boiling water bath.

Experiment 8.

The very strong fumes of ammonia which were always noticed upon opening the bomb indicated the presence of water in the materials used. The alcohol ordinarily had been rendered absolute by refluxing over lime and distilling. In the present run this so-called absolute alcohol was further dried by adding sodium (5 gr. per liter) shaking violently while the sodium was reacting. The alcohol was then distilled on a water bath leaving the sodium hydroxide and sodium ethylate in the flask. Furthermore the urea used was dried at 110° for 6 hours.

The proportions used were 100 grams ester, 60 grams urea, 48 grams sodium, and 900 grams ethyl alcohol. The batch was mixed and allowed to stand 48 hours, then heated for 5 hours in the autoclave at $105-110^{\circ}$. Throughout the mixing and handling every precaution was taken to exclude water. A different procedure was also used in precipitating the veronal from its sodium salt. After filtering off the solid from the alcohol, it was dissolved in a dilute HCl solution (400 cc. H_2O 38 cc. concentrated HCl) and heated to boiling. On cooling at first the veronal did not precipitate but on adding a very little acid the entire liquid flocked out. This was filtered and proved to be almost pure veronal with practically no Na Cl. From this run 40 grams of product were obtained, or 47% of theory. This was by far the most successful run made, the success probably being due to the absolute exclusion of water and allowing the mixed components to stand before heating.

Preparation of Benzyl-ethyl-malonic Ester.

Benzyl malonic ester was prepared after the method of Noyes¹⁴ with somewhat different proportions.

23 grams of metallic sodium were dissolved in 500 cc. of absolute alcohol. After cooling 126 grams of benzyl chloride were added in small portions and with constant shaking. The mixture was then heated with a reflux condenser on a water bath until it reacted neutral to litmus (3 hours). Enough water was added to dissolve the Na Cl and the solution extracted with ether. The ether solution of benzyl malonic ester was dried with anhydrous sodium sulphate and distilled under diminished pressure. The product came over at 188-192° C.

The ethyl group was next introduced according to a method resembling that used by Conrad¹⁵. One mole of sodium (23.05 gms.) was dissolved in 300 cc. absolute alcohol and to the cooled sodium ethylate was added with constant shaking, one mole of benzyl malonic ester (250 gr.). The sodium ethylate formed more or less of a solid cake in the flask, which dissolved slowly. To the yellow red liquid, in the course of about an hour was added with shaking, 1.28 moles (200 gms.) of C_2H_5I . The mixture was allowed to stand over night and then heated on the steam cone for a short time. The alcohol was distilled off on a water bath and after cooling enough water added to dissolve the Na I. The water solution was extracted with ether twice and the excess iodine destroyed by adding a water solution of sodium thiosulfate. The ether layer was separated, extracted with water, dried with sodium sulfate and distilled under diminished pressure. The product

came over at 180-188⁰ under about 20 mm. pressure. 153 grams were obtained.

Preparation of Benzyl Ethyl Barbituric Acid.

No instance could be found in the literature where benzyl ethyl barbituric acid had ever been made, consequently a procedure analogous to the one of Fischer and Diltthey⁹ for the preparation of di benzyl barbituric acid was used.

The proportions used were:-

4.7 grams Na

75 grams absolute alcohol

16 grams benzyl ethyl malonic ester

4.8 grams urea.

The absolute alcohol was further dried with sodium and the urea dried at 110⁰ for 6 hours. The mixture was allowed to stand 48 hours then sealed in bomb tubes and heated in an oil bath for 5 hours at 106-108⁰. The white precipitate of Na₂CO₃ was filtered off and the filtrate distilled under diminished pressure until all the alcohol was over. The liquid left in the distilling flask was of a very thick gummy nature and upon acidifying it with concentrated HCl a white flocculent precipitate of benzyl ethyl barbituric acid separated out.

The product was filtered and recrystallized from 50% ethyl alcohol. After three recrystallizations it melted constant at 212-213⁰ C. The compound was dried at 110⁰ and analyzed by combustion for carbon and hydrogen. The results of the analysis were,

21.

Wt. of sample taken	.2070 gms.
Wt. of CO ₂ absorbed	.4846 "
Wt. of H ₂ O absorbed	.1119 "

	Calculated	Found
Percentage of Carbon	63.4	63.80
" " " Hydrogen	5.69	6.04

Summary.

Methyl alcoholate can be used as a condensing agent in the synthesis of diethyl barbituric acid and presents the following advantages over ethyl alcoholate:

- A. Increases the capacity of apparatus.
- B. Permits the use of a boiling water bath for heating the autoclave.

Absolute exclusion of all moisture is essential to the success of the veronal synthesis.

The various components should be allowed to react in the cold for at least 48 hours before heating in the autoclave.

A technical grade of urea made by the American Cyanamid Co. was tried and gave just as satisfactory results as the chemically pure product.

Experiments were tried using different proportions of sodium and the best results were obtained with three moles, as was stated by Fischer and Diltthey.

Benzyl ethyl barbituric acid, a new compound was synthesized and analysed.

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